Thomas[17] in 1963 estimated that 25% of all barium enemas then given in the U.S.A. contained tannic acid. A further refinement of its application to radiology was the addition of tannic acid to the preparatory enemas, preceding the tannic acid barium enemas.

Although there was evidence of hepatotoxicity when tannic acid was used in burns there were no suggestions that tannic acid could be absorbed from the colon and damage the liver until 1963.

In that year McAlister, Anderson, Bloomberg and Margulis[18] reported on the lethal effects of tannic acid in the barium enema. The concentration of tannic acid recommended for use in barium enema examinations varied between 0.25 and 3.0 per cent.

A patient at the St. Louis Children's Hospital died with acute hepatic failure, and a search for possible hepatotoxic agents uncovered only the tannic acid added to the barium sulfate suspension used in the roentgen examination of the colon and in the preparatory enemas for that examination. Tannic acid was demonstrated in the liver of this patient. They were unable to discover either experimental data on the absorption of tannic acid from the colon and terminal ileum or reports of fatalities or serious complications associated with its use in the gastrointestinal tract. This case was reported as an example of death due to liver failure as a result of the absorption of tannic acid from the intact bowel, together with two other cases with hepatic necrosis found in a review of sudden, unexplained deaths after the performance of a colon examination. These deaths occurred over a twelve-month span. In addition, experimental

studies were undertaken to confirm the absorption of tannic acid from the colon and to show its effect on the liver.

Case Reports

Case 1. Clinical Course: A 10 year old white boy was admitted to the St. Louis Children's Hospital because of abdominal cramping associated with urgency and fecal incontinence of several months duration. The next morning he received two preparatory saline enemas and one barium enema all three containing 0.75 per cent concentration of tannic acid. Poor evacuation of the barium sulfate was observed. There was reflux into the terminal ileum. On the third hospital day four normal saline enemas were given in the early morning prior to an upper gastrointestinal series. This examination was within normal limits. The colon did contain residual barium. On the fourth hospital day vomiting occurred three times but no clinical cause was apparent.

On the morning of the seventh day the central nervous system symptoms and renal depression persisted. The patient did not appear jaundiced at this time, but liver function tests showed severe hepatic damage. The patient became rapidly and deeply jaundiced with progressive oliguria. Treatment with hydrocortisone and peritoneal dialysis was attempted for eighteen hours before death in the morning of the eighth day, five days after the first symptoms of vomiting appeared.

Autopsy. The liver weighed 780 gm. and on the cut surface exhibited a typical nutmeg appearance. Nessler's reagent was applied to the fresh tissue and an immediate positive reaction was obtained, indica-

ting the presence of tannic acid. Microscopically, there was pronounced centrolobular atrophy with necrosis and congestion. A diffuse neutrophile infiltrate involved the entire liver lobule with central and portal lymphocytic accumulations. Only a few relatively normal hepatic cells remained around the portal areas. Coarse droplets of fat and fatty cysts were found in the periportal areas and finer fat droplets appeared in the hepatic cell cytoplasm in the central portions of the lobules. In the periportal liver cells there were nuclear pyknosis and irregularity. Focal bile stasis was seen. New cellular regeneration was present and there was an increase in connective tissue.

Case II. A 4 month old white girl was admitted to the St. Louis Children's Hospital because of constipation. A barium enema examination with tannic acid (0.75 per cent) was performed nine days after admission. The following day persistent vomiting occurred with dehydration. The patient went into shock without apparent adequate clinical cause and died forty-eight hours after the barium enema. Liver function tests were not obtained.

Autopsy: The liver weighed 185 gm. and was pale. Microscopically, it showed marked atrophy and degeneration of the hepatic cells throughout the lobules. An abundant quantity of cytoplasmic fat was present predominantly in fine droplet form. Slight sinusoidal congestion was seen without much neutrophilic infiltrate or accumulation of nuclear débris. There was no evidence of cellular regeneration or bile stasis.

Case III. A 5 year old white girl was admitted to the St. Louis Children's Hospital because of a history of recurrent abdominal pain. On the third day one preparatory and one barium enema were given, both containing tannic acid (0.75 per cent). The patient vomited seven times later that day without apparent cause. The following day she was given nothing by mouth after midnight in preparation for an upper gastrointestinal series but this examination was cancelled because of residual barium sulfate in the colon. She was febrile that afternoon and vomited once. The next day bloody vomiting occurred. The child rapidly became lethargic, incoherent, disoriented, and hypotensive. She died within hours after the onset of cerebral symptoms and cardiovascular collapse. Death occurred seventy-two hours after the barium enema.

Autopsy: The liver was pale and weighed 570 gm. Microscopically there was slight disorganization of the architecture with numerous intracytoplasmic droplets and many fatty cysts. A slight diffuse neutrophilic infiltrate was encountered throughout the lobules but was more pronounced in the portal areas where a few lymphocytes were also evident. Hepatic cell nuclei were frequently pyknotic, and a moderate amount of nuclear débris was seen. The sinusoids were slightly congested, especially in the central region where the hepatic cell cytoplasm stained more lightly with eosin than usual. No bile stasis and no regeneration were evident.

Twelve male albino rats weighing 400 to 500 gm. were anesthetized with ether, and either a 1 per cent or 5 per cent solution of tannic acid was administered by rectal tube and syringe. The larger part of the

solution was immediately expelled. The animals were killed by decapitation at fifteen, forty-five, and ninety minute intervals following the enemas. Control or blank plasma was obtained from animals which received no enema. Demonstrable amounts of tannic acid (plus gallic acid) were absorbed in both groups of animals which had been given tannic acid. There was detectable material in the plasma at fifteen minutes in both groups, a greater amount being absorbed with the 5 per cent solution.

The distal colon was examined histologically and showed a progressive diminution in the amount of stainable mucin over the experimental time period. There was disruption in the apical plasma membranes of the luminal goblet cells; however, this did not extend to involve the cells of the crypts. Histologic alteration of the liver was not demonstrated over the time period of this experiment, but in another group of rats there was some accumulation of intracytoplasmic fat in the periportal areas forty-eight hours after either a 1 per cent or 5 per cent tannic acid enema.

A similar group of animals was given 1 per cent tannic acid enemas and killed at varying time intervals up to three hours following colonic irrigation. Portions of fresh liver, kidney, spleen, lung, and mesentery were examined with Nessler's reagent for the qualitative presence of tannic acid. All these organs proved to be negative when tested in this manner. The mucosal surface of the colon, however gave a positive reaction throughout the three hour time period.

The Nessler's reagent is not specific for tannic acid. It will react with a number of phenolic bodies as well as with acetone and

ammonia. It is, however, a sensitive detector of tannic acid. Normal livers or livers damaged by agents other than tannic acid did not give a positive reaction with Nessler's reagent. Seven rats in which liver necrosis (histologically confirmed) was produced with carbon tetrachloride gave a negative Nessler's test. The same negative finding was encountered on liver biopsy or at autopsy in human beings with normal liver, hepatitis, chronic renal failure, and in a lymphosarcoma patient with hepatic and renal involvement.

Rats that had 5 per cent tannic acid introduced per os showed a positive reaction in the liver with Nessler's reagent, and the same findings in the liver were encountered when 50 per cent tannic acid was introduced intraperitoneally or intramuscularly. In the latter animals the Nessler's reagent also gave a positive reaction locally at the site of the intramuscular injection.

Either 1 per cent or 5 per cent tannic acid-barium sulfate enemas were administered to a series of 8 dogs (4 in each group), with and without reflux of the contrast material into the ileum. These examinations were carried out under fluoroscopic control. Absorption levels in the 5 per cent group ranged from trace amounts up to 14.2 mg. per cent of tannic acid in the plasma. Plasma levels were detectable over the entire time period of the experiment--thirty minutes, one, two and three hours. The 1 per cent group did not show detectable plasma levels. The presence or absence of ileal reflux did not seem to correlate with the plasma levels. In 4 of 8 dogs, liver biopsies were obtained percutaneously prior to the tannic acid enemas and repeated forty-eight hours after the enemas. The

latter specimens showed intracytoplasmic fat droplets, fatty cysts, centrolobular necrosis with nuclear pyknosis, and sinusoidal congestion in 2 dogs receiving 5 per cent tannic acid enemas. One dog died the same day the liver biopsy was performed. Accumulation of intracytoplasmic fat in hepatic cells was present in 1 of the 2 dogs biopsied after 1 per cent tannic acid enemas.

Also in 1963 an article appeared by Lucke, Hodge and Patt[19]. In October 1962 a 9 year old boy died at the Chedoke General and Children's Hospital, Hamilton, Ontario, from acute liver failure. There was no known contact with cases of infective hepatitis and no history of recent infection, or of exposure to hepatotoxic agents. The patient had received a barium enema two days before death, but the possible etiological role of its tannic acid content was not immediately appreciated. Autopsy was refused and death was ascribed to viral hepatitis.

Five months later, on the occasion of a second acute liver death, that of a 2 year old girl, the possible role of the tannic acid content of the barium enema was considered. Three other deaths from fulminating liver failure, since the opening of the Chedoke General and Children's Hospital, in December 1960, were then recalled and perusal of the records revealed that each of these patients had received a barium enema containing tannic acid one to six days before death.

In April 1963 the summary of a forthcoming article by McAlister et al[18] and an editorial by Thomas[17] became available, each discussing

the possibility of liver damage resulting from the use of barium enemas containing tannic acid. This prompted the authors to re-examine the five fatal cases of liver failure referred to above, from the point of view of their deaths being related to tannic acid exposure.

From March 1962 on, a Clysodrast cleansing enema containing 0.25% tannic acid and administered early on the morning of examination was added to the routine preparation consisted of purgation late on the day preceding the barium enema. This was not given to patients under the age of 16 years. Consequently, only two of the five patients received a Clysodrast enema before the barium enema. The barium sulfate suspension was prepared to contain 2% tannic acid.

Details of the five cases showed that the course of events following the barium enema was similar in three patients (Cases 1, 3 and 5). Having received the enema in midmorning they were well until late the same day or early the next morning when their terminal illness set in, with vomiting and abdominal pain.

Autopsy findings, with minor variations, were similar in the four cases examined and, in particular, there were no abnormalities that could be related to the complaints which had brought these patients to the hospital. Icterus was present except in Case 2, where the interval between enema and death had been shortest. Generalized hemorrhagic manifestations were seen in all four. Liver damage was the single finding of importance in all instances. The livers ranged from moderately swollen and firm (Case 5) to flabby and shrunken (Case 4). No portions of any of these

livers were spared by the process. All stages of parenchymal cell death, with fatty change a constant finding, were seen. Although virtually the entire liver lobule was involved, the more advanced degree of destruction around the central vein and the survival of some peripheral cells pointed to a centrilobular type or degeneration and necrosis. Cellular reaction was minimal, except in Case 4, where there were numerous intralobular and portal neutrophils, mononuclear cells and some eosinophils, as well as a marked proliferation of bile ductules. Tannic acid is no longer employed in barium enemas.

CLAIMS

Tannic acid is claimed to be effective for the treatment of dermatitis caused by poison ivy and related plants; for the treatment of ingrown toenails; and for the treatment of herpes simplex lesions. These claims are examined below.

Submission #160076

The product described herein is advised for the relief of dermatitis caused by members of the Anacardeaceae family. The directions state that the material is to be applied to the affected parts. There is no suggestion that large areas of involved skin may not be so treated.

With respect to supporting data the bibliography is grossly inadequate. The submission refers to a search of Chemical Abstracts from 1907 to 1972. It does not refer to a search of medical literature and

cites none of the published articles referred to above. The company does offer data as to the toxicity of tannic acid when administered per os to rats. No evidence for safety when applied to denuded skin is offered. Reference is made to a Federal Security Agency Public Health Service publication, Health Information Series No. 65, dated 1949 which recommends repeated application of tannic acid to: "but a few small blisters on the hands, arms, or legs...if large (blisters) form go to your doctor". There is also a photocopy of Public Health Reports for May 16, 1941 on the treatment of poison ivy dermatitis with tannic acid. No studies for possible toxicity are included in this article, except for the article of Dr. Louis Schwartz referred to, which encompasses 11 patients, one of whom failed to return. There are no data to support claims made except those of an anecdotal nature from satisfied customers.

Recommendation: Tannic acid solutions are demonstrably toxic when applied to large areas of denuded skin as in the case of severe contact dermatitis but are probably safe when applied to quite limited areas. This could be determined by animal experimentation as contact dermatitis is readily induced in guinea pigs with 2, 4 dinitro benzene compounds.

It is considered that its efficacy has not been established.

Submissions 160023, 160024

Minor wounds

These products are recommended by the manufacturers for the treatment of minor wounds. It is claimed that the tannic acid helps

precipitate protein in abraded tissue forming a protective coating, and thus checking excessive secretion and stopping superficial hemorrhage. These claims seem reasonable and it is recommended for inclusion in Category 1 with respect to them.

Submission 160013

Herpes simplex

No claims are contained in this submission and there are no labels. An inference may be derived from a letter from a chemical consultant that the ingredients contained in the product are safe and efficacious in the treatment of cold sores. An ipse dixit of this sort is not convincing evidence. As cases of herpes simplex are legion the matter of efficacy can easily be established. The small amount of tannic acid present seems not to be dangerous.

Recommendation: Efficacy unproven.

Submission 5-016-127

Ingrown toenails

Claim is made that this product gives fast temporary relief of pain associated with ingrown nails. This claim is justified by two clinical trials, the first of which is somewhat deceptive in that 80 patients are stated to have been treated for ingrown toenail. In point of fact perusal indicates that only 15 were so treated the other 65 patients having such disorders as callused nail grooves, fungus infections and so on.

The second study by a podiatrist and a dermatologist comprises 44 cases and is valid.

Three letters from certified dermatologists state that in their opinion the formula is safe and effective as well as non irritating. These statements seem acceptable. Each letter goes on to say that "I believe that other qualified experts in the field will concur with my interpretation". These statements of opinion, considered to be held by other persons none of whose views appear to have been solicited, are valueless, null, void and nugatory.

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APP-16.1

SUMMARY MINUTES OF THE OTC REVIEW PANEL
ON MISCELLANEOUS EXTERNAL DRUG PRODUCTS

Fifteenth Meeting
January 14 and 15, 1976

Conference Room K
Parklawn Building
Rockville, Maryland

and

Connecticut Room
Holiday Inn
Bethesda, Maryland

Panel Members

William E. Lotterhos, M.D., Chairman
Chester L. Rossi, D.P.M.
Rose Dagirmanjian, Ph.D.
Harry E. Morton, Sc.D.
George C. Cypress, Jr., M.D.
Marianne N. O'Donoghue, M.D.

Liaison Representatives

Consumers
Marvin M. Lipman, M.D.

CTFA
Saul A. Bell, Pharm.D.

Proprietary Association
Bruce Semple, M.D.

FDA Representatives

John Davitt, Executive Secretary
Michael Kennedy, Panel Administrator
Victor Lindmark, Pharm.D., Drug Information Analyst

Statements made herein are provisional in nature and may be modified or revised in subsequent meetings of the Panel or in their final complete report to the Commissioner.

Whenever there is a lack of unanimity on any given point, the vote will be given. Regulations do not permit voting by the Liaison Members, Consultants, or FDA Staff Members.

Adopted 28 Feb 1977

Wm E. Lotterhos, M.D.
Chairman

The Panel met in open session. There were no requests for presentations. Only one guest was present, Ms. Michelle Deschenes, of the Pink Sheet. The following ingredients were discussed during the meeting:

ACETONE: The Panel is still concerned about the possible cataractogenicity potential of topically applied acetone. It is felt that any retrospective study, e.g., in exposed industrial workers, would be complicated by the high spontaneous incidence of lenticular changes in humans.

ALLANTOIN: The initial draft of a Panel report was discussed. The Panel is considering placing allantoin into Category I as a keratolytic emollient and debriding agent at concentrations of 0.5 - 2 percent.

ZIRCONIUM COMPOUNDS: An Industry liaison provided a preprint of a report by Dr. John Turk (Royal College of Surgeons) on the potential for granuloma promotion by compounds containing zirconium and some other metals. The two compounds of concern to the Panel, zirconium oxide and carbonate, are not dealt with in this report. However, a Panel member met with Dr. Turk on a recent trip to England and brought back an informal report dealing in part with zirconium carbonate experiments in guinea pigs. It appears that insoluble zirconium salts such as the carbonate fail to produce granulomata upon intradermal administration, while soluble salts such as zirconium lactate do. The antiperspirant agents ZAGS and aluminum chlorhydrol were found to

cause thickening of the skin in these experiments, wheras zirconium carbonate did not.

CAMPHOR: A revised draft of the Panel report was presented and commented upon. The final report is not yet complete. However, the Panel is very much concerned about the relatively numerous reports of serious poisonings (e.g., through accidental ingestion) by camphor-containing preparations such as camphorated oil. This ingredient has been placed in Category II with regard to antipruritic, analgesic, local anesthetic, antimicrobial and all other claims except rubifacient counterirritant.

OIL OF EUCALYPTUS AND OTHER ESSENTIAL OILS: A preliminary report was presented. There seems to be little information available to suppo safety and efficacy of these ingredients for any particular indication. Almost invariably they occur in multiple ingredient drugs and the Panel has not yet decided how to deal with evaluation of such combinations. Tentatively, the Panel placed oil of eucalyptus in Category III for antiseptic claims.

UREA: A Panel member presented a report concerning urea and some related ingredients.

In connection with a discussion of possible revision in the Panel's working procedure, it was agreed to circulate a fixed agenda as far in advance of the next meeting as possible in an attempt to speed up debate.

The next Panel Meeting is scheduled for February 27-28, 1977. The subjects to be discussed will be acetone, camphor, talc, Urea, Vitamin A and D (topical), Oil of Cade, Juniper tar and Passion fruit.

A Panel meeting is also tentatively scheduled for April 2 and 3, 1977.

SUMMARY MINUTES OF THE OTC REVIEW PANEL
ON MISCELLANEOUS EXTERNAL DRUG PRODUCTS

Sixteenth Meeting
February 27 and 28, 1977

Georgia Room
Holiday Inn
Bethesda, Maryland

and

Conference Room C
Parklawn Building
Rockville, Maryland

Panel Members

William E. Lotterhos, M.D., Chairman
Chester L. Rossi, D.P.M.
Rose Dagirmanjian, Ph.D. (absent)
Harry E. Morton, Sc.D.
George C. Cypress, Jr., M.D.
Marianne N. O'Donoghue, M.D. (absent)

Consultants
Albert A. Belmonte, Ph.D.

Liaison Representatives

Consumers
Marvin M. Lipman, M.D.

CTFA
Saul A. Bell, Pharm.D.

Proprietary Association
Bruce Semple, M.D.

FDA Representatives

Michael Kennedy, Panel Administrator
Victor Lindmark, Pharm.D., Drug Information Analyst
George James, Acting Executive Secretary (2/28/77)

Statements made herein are provisional in nature and may be modified or revised in subsequent meetings of the Panel or in their final complete report to the Commissioner.

Whenever there is a lack of unanimity on any given point, the vote will be given. Regulations do not permit voting by the Liaison Members, Consultants, or FDA Staff Members.

Adopted [illegible] 1977

[illegible]

5 Pages

Summary Minutes

February 27, 1977

The meeting was called to order at 9:15 a.m.

Two consultants, Dr. A. A. Belmonte and Mr. J. Tanja of the Auburn University, School of Pharmacy were approved and appointed to the Panel. These consultants may aid panelists in the collection of information through the use of the computer literature search facilities of Auburn University, the preparation of work papers and initial drafts on ingredients for presentation to the Panel and in the final preparation of monographs.

Dr. Belmonte attended the meeting and was introduced to the Panel. A discussion of methods currently used by the panelists in preparing initial work papers ensued. Recognizing that much of the information utilized by the Panel is derived from industry submissions, concern was raised regarding the time gap between the time of submission by industry and the time at which the Panel reviews the information, which may be as much as three years. It was suggested that an up-to-date literature search be conducted on each ingredient under review.

Camphor. Additional information was presented to the Panel on camphor. It was reported that camphor can be metabolized by certain micro-organisms and that this would weaken any antimicrobial claims for it. Weak evidence was presented that camphor had weak counter-irritant activity.

It was recognized that camphor is a mutagen. At a recent, joint meeting of the Theobald Smith Society of New Jersey and the Eastern Pennsylvania Branch of the American Society for Microbiology, three speakers addressed an in-vitro carcinogenicity screen testing on the relationship between mutagenesis and carcinogenesis. These investigators found, using strains of E. coli, S. typhimurium and Neurospora, an 87 percent probability that if an agent is mutagenic, it is also carcinogenic. The agents were, unfortunately, not revealed. A panelist will attempt to provide the Panel with more detailed literature on this subject.

A clarification on the difference between active (pharmacologically) and inactive (pharmaceutically active) ingredients followed. For the purposes of the Panel's review, all ingredients claimed by the manufacturer to be active shall be reviewed for the particular labeling claims made for it with respect to safety and efficacy. However, the Panel is free to review for safety, any inactive ingredient(s), combination of ingredients or labeling claim for which a potential safety problem may exist.

The monograph on ketones was adopted by the Panel and is appended to this set of minutes. The "Evaluation of Drugs Containing Camphor" was also adopted by the Panel.

Urea. A report on urea was presented to the Panel. The antipruritic and skin softening claims were addressed. Although urea was not submitted as a debriding agent, the industry liaison suggested it might be reviewed for the purpose. The Panel deferred tentative judgement on urea until more up-to-date literature, recently provided to the Panel, could be evaluated and incorporated into the report. The report was accepted for information.

Oil of turpentine. A report on oil of turpentine based on information obtained from the FDA's Panels on Hemorrhoidal preparations and Topical Analgesics was presented to the Panel. None of the previous Panels reviewed oil of turpentine as an antiparasitic or hemostat (claims made for it in an industry submission). A formal presentation to the Panel will be made on oil of turpentine at the next meeting.

A statistical evaluation by the FDA, Division of Biometrics was distributed to the Panel on a submission of triethanolamine and benzalkonium chloride. The evaluation was accepted by the Panel for information.

Results of the consultants preliminary reviews of adopted Panel reports followed.

Pediculocides. All delousing ingredients, combinations and labeling claims have not yet been completely addressed. Additional work will be needed before final editing can proceed.

Tannins. It was suggested that recommended labeling and combination products containing tannins be considered before work proceeds.

Hydroquinone. The Panel will need to set a lower limit on concentration and recommended labeling will require further work.

The Panel's review on the alcohols is relatively complete. The Panel will now begin a review of acids used in antimicrobial products. Once this is completed, acid-alcohol drug combinations will be considered for antimicrobial claims.

Panel assignments were made for further work on the following ingredients:

urea	zirconium
pine tar oil	denatonium benzoate
vitamins A and D	passion fruit

Also, work will continue on the Panel's "Guidelines for Evaluation" of ingredients.

Dates for future Panel meetings were set for:

17th April 3 and 4 beginning at 1:00 p.m. on the 3rd.

18th June 5 and 6 beginning at 1:00 p.m. on the 5th.

February 28, 1977

The meeting was called to order at 9:15 a.m.

Dr. George Rogers, Vice President and Medical Director of Breon Laboratories, Sterling Drug, Inc. discussed some of the toxicity studies being conducted on Camphor-Phenique. A question and answer period followed. A panelist commented that there is no evidence in the submission on Camphor-Phenique supporting antiseptic and fungicidal claims made for it. Further, it was stated that a 1:100 dilution killed Herpes simplex virus but that it also killed the tissue cells as well. Another panelist inquired about any studies on photosensitivity of the product. Dr. Rogers was not aware of any such data, but said he would submit additional data to support these claims in response to enquiries.

The minutes of the 15th meeting were read and approved.

Talc. A report on talc was presented to the Panel. Material on the toxicology of talc from the Antiperspirant Panel was read. The Antiperspirant Panel adopted the current Cosmetic, Toiletry and Fragrance Association (C.T.F.A.) standards for cosmetic and industrial grade talc. They concluded that industrial grade talc, because of its possible asbestos content, was to be placed in Category II for safety. The Panel decided to write a formal monograph for talc. The Antiperspirant Panel paper was accepted for information.

The meeting was adjourned at 11:00 a.m.

TENTATIVE DRAFT REPORT

OF

THE OVER-THE-COUNTER MISCELLANEOUS EXTERNAL DRUG PRODUCTS

REVIEW PANEL ON THE ANTIMICROBIAL PROPERTIES OF KETONES

KETONES

Ketones are a group of chemical compounds containing the carbonyl group, $-\overset{O}{\overset{\|}{C}}-$, in union with two carbon atoms. When two hydrogen atoms are removed from a secondary alcohol by oxidation, a ketone is produced. When a primary alcohol is oxidized an aldehyde is produced. Upon further oxidation a ketone yields the acid corresponding to the secondary alcohol. Like the alcohols, ketones of low molecular weight are liquids and those of high molecular weights are solids. The simplest ketone, acetone, is a solvent for oils, fats and other chemicals and has been shown to have antimicrobial activity.

Three ketones, acetone, methyl isobutyl ketone and camphor, by themselves or in combination with other substances, are official denaturants for alcohol (Ref. 1). Many preparations containing ketones come in contact with the human body in a wide variety of drugs, cosmetics, solvents, industrial chemicals, etc.

The Ketones comprise a large class of chemical compounds and in general are weaker in antimicrobial acivity than are the alcohols (Ref. 2). Only those present in products submitted to the Panel for reviewing Over-the-Counter Miscellaneous External Drugs will be discussed and then principally from the standpoint of their antimicrobal activity.

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1. Acetone (Dimethyl ketone)

Acetone is a colorless, transparent, volatile, highly flammable liquid (flash point - 20°C), with a pungent, sweetish taste and a characteristic odor. It is miscible with water, alcohol, ether, chloroform and most oils. It is widely used as a solvent for oils, fats, waxes, resins, plastics, etc. It is used as a topical cleansing agent, especially before dermal vaccination because of its solvent action and rapid and complete evaporation (Refs. 1 and 2).

Clinicians often place diagnostic significance on the detection of acetone in the breath of patients in diabetic coma and the ability to detect the vapors of a toxic chemical, such as acetone, is important to the safety of individuals handling or exposed to chemicals. However, the sensitivity of the sense of smell for acetone varies among individuals.

Among 151 individuals ranging in age between 15 and 39 years there was a trimodal distribution for the thresholds for the ability to smell acetone. The peaks were at 1.0, 0.25 and 0.05 percents. There was no difference between the thresholds for males and those for females but there was between those for this group and the thresholds for older individuals. Among 60 individuals ranging in age between 40 and 69 years, there was a bimodal distribution for the threshold which were at 2.0 and 0.5 percents. Since there were no nontasters

of phenylthiocarbamate (PTC) among those individuals with the most sensitive sense of smell for acetone and 26 percent nontasters among those individuals with the least sensitive sense of smell, the authors suggested a genetic basis for the ability to smell acetone. In addition, the authors point out the possibility of genetic linkgage for the abilities to smell acetone and taste PTC (Ref.3).

Inhalation is the most likely mode of contact during industrial handling and use as a solvent, due to the high volatility of acetone. Inhalation of acetone vapors may produce headache, fatigue, excitement, bronchial irritation, and in large amounts, narcosis (Ref. 1). In addition, nausea and vomiting may be symptoms (Ref. 4). The maximum allowable atmospheric concentration of acetone is 500 ppm (Ref. 5). The threshold limit value (TLV) in air is 1,000 ppm. Exposure to 1,600 ppm for 15 min causes irritation of eyes and nose and sometimes nausea and dizziness (Ref. 6). Individuals exposed for short periods (3 to 5 min) reported that acetone vapors 300 ppm produced slight irritation to the eyes, nose and throat and a concentration of 500 ppm was tolerated by most individuals (Ref. 36). Single exposures inhaling 46,000 ppm acetone vapors for 1 hour were fatal for mice and 42,400 ppm for 4.5 5.5 hours were fatal for rats (Ref. 7).

The oral LD_{50} for rabbits is given as 5.34 gms per kg and for rats it is 9.5 gms per kg (Ref. 8).

The topical application of acetone to normal human skin produced only mild edema and hyperemia, clinically, but by electromicroscopy changes were observed mainly in the stratum corneum and stratum spinosum (s. mucosum or s. malpighii). Marketed intracellular edema of keratinized cells and vaculation of spinous cells were seen after exposure to acetone for 30 minutes. The changes were more marked after exposure for 90 minutes. No ultrastructural changes were observed in the basal layer, cells of Langerhans or melanocytes. Seventy-two hours after the discontinuance of the 90 minute application of acetone, a high degree of restoration of the normal ultrastructural pattern was observed in the superficial layers and evidence of early reactive changes were observed in the viable portion of the epidermis (Ref. 9).

Since acetone is a lipid solvent, its injurious effect upon the skin may be due mainly to removal of lipids present in the stratum corneum and thus disrupt the lipoproteins. Electron autoradiographic studies demonstrated that acetone markedly impaired protein synthesis (Ref. 10). The deleterious severe ultrastructural changes in the skin produced by acetone could be prevented by the concomitant application of a protective cream (Ref. 11).

Chemical burns of the human cornea caused by acetone are rare and those reported healed within 48 hours (Ref. 37). Acetone produced less severe burns of rabbit cornea than ethanol, isopropanol or methanol (Ref. 38).

It is stated that acetone has a low order of sensitizing potential (Ref. 12) and the paucity of reports on allergic reactions to acetone bear out this statement. Acetone, along with other ketones, is stated to be the safest solvent employed for dissolving resins and other substances for patch testing.

Four cases of acute acetone poisoning have been reported following the application of plastic casts that utilized acetone during their application (Refs. 13, 14, 39 and 40). In these particular cases it is not clear if the acetone entered the body by way of the lungs or through the skin or by both routes. After having entered the body the elimination of acetone in exhaled air and in urine is very slow (Ref. 41) and high blood levels may be maintained for many hours (Ref. 40). It is metabolized in the body but at a much slower rate than that of ethanol (Ref. 43). Work with guinea pigs demonstrated that acetone can enter the body following topical application or by subcutaneous injection, enter the general circulation and produce pathology in the eyes (Ref. 15).

Acetone, 0.5 ml was dropped directly onto the skin of 12 guinea pigs 3 times per week for 3 weeks. Two of the 12 guinea pigs developed extensive vacuolated areas involving the entire periphery of the lens.

Another group of 12 guinea pigs was injected subcutaneously with 0.05 ml acetone-saline (1:1) solution 3 times per week for 3 weeks. One developed extensive vacuolated areas involving the entire periphery of the lens and one developed isolated vacuolated areas in the periphery of the lens. Another group of 12 guinea pigs was injected subcutaneously with 0.05 ml of a solution of 5 percent acetone in saline 3 times per week for 3 weeks. One animal developed extensive vacoulated areas involving the entire periphery of the lens and 4 guinea pigs developed isolated vacuolated areas in the periphery of the lens. Thus, 9 or 25 percent, of the 36 guinea pigs exposed to acetone developed cataracts. More of the guinea pigs developed cataracts from acetone than from cyclohexanone, another ketone, or diemthyl-sulfoxide (Ref. 15).

Young rats, 25 days old, were fed powdered stock pellets to which were added 5 or 10 gms mimosine, a ketone with the formula β(3-hydroxy-4-pyridone)-α-aminopropionic acid. After a few days on the diet a syndrome of stunted growth, ruffling and loss of hair, and ocular lesions were produced. Cataractous changes occurred within 3 days on the diet and were accompanied by extensive inflammatory signs of the cornea and iris. In the later stages there was disorganization of the lens histology and full cataracts developed (Ref. 16). As with the guinea pigs, the toxic substance reached the eyes of the rats by way of the blood stream.

No information has been found pertaining to the susceptibility of human ocular tissue to prolonged exposure to acetone. However, the human lens appears to frequently show some form of decreased transparency.

Among 300 men, most of whom were candidates in the Royal Air Force, selected at random and not complaining of ocular symptoms, examined without mydriasis and under a magnification of ten-fold, the total incidence of cataract was 94.3 percent. The ages ranged from 19 to 60 years with an average of 28.2 years. Many of the men displayed more than one form of opacity. Using the term cataract to mean any decrease in transparency of the lens the various types of cataracts and their frequencies were as follows:

Scattered dots (one or more dots of opacity in one or both lenses, involving cortex or adult nucleus or both) 279 cases, 93 percent.

Multiple dots in fetal nucleus, 65 cases, 21.7 percent.

Coronary cataract, 18 cases, 6 percent (the average age of this groups was 35.2 years). In a randomly selected series of 100 men, whose average age was 27.7 years, examined with mydriasis and the slit lamp, there were 23 cases of coronary cataract.

Anterior axial embryonic cataract, 12 cases, 4 percent.

Dilacerated cataract, 4 cases.

Suture cataract, 3 cases.

Anterior capsular cataract, 3 cases.

Senile catract, 1 case.

Of the noncataractous condition there were 58 cases with epicapsular pigment, 42 cases with persistent pupillary membrane and 10 cases with fluid vacuoles (Ref. 42).

The following dilutions of acetone inhibited the growth of Escherichia coli, Pseudomonas fluorescens non-liquefaciens and Staphylococcus cremoris viscosi for 48 hours at 37°C 1:11, 1:19 (Ref. 17) and 1:10 (Ref. 18), respectively, thus indicating a preservative or bacteriostatic action. A dilution of 1:4 was germidical for Staphylococcus cremoris viscosi giving it a phenol coefficient of 0.02 (Ref. 18).

Against Salmonella typhosa acetone had a phenol coefficient of 0.04 and against Staphylococcus aureus, 0.036. These coefficients are practically the same as for ethyl alcohol and the same two microorganisms (Ref. 19). A phenol coefficient of 0.03 for acetone and S. aureus was obtained by others (Ref. 20). Acetone in 95 and 85 percent concentrations killed S. aureus in 5 sec and concentrations of 75 and 65 percent killed in exposures of 30 sec. Thus, high concentrations of acetone are required for the rapid killing of vegetative bacterial

cells. Undiluted acetone has poor sporicidal activity as spores of Bacillus subtilis remained viable after exposure to acetone for 4 days (Ref. 20). In its ability to remove bacteria from skin undiluted acetone was found to be inferior to 70 percent ethyl alcohol (Ref. 20).

In addition to acetone exerting a germicidal action against Salmonella typhosa, the Vi antigen, which is so important for the production of protective antibodies, is not lost during the sterilization and drying with acetone and a better vaccine results (Refs. 21 and 22). The acetone appears to fix the Vi antigen to the bacterial cells (Ref. 23). Organisms of many of the serotypes of Klebsiella killed and dried with acetone appeared to have their capsules better preserved and a good vaccine results (Ref. 24).

Many viruses are susceptbile to the action of lipid solvents and surface active agents and, indeed, ether lability is one of the properties of viruses employed for their identification. Acetone being a lipid solvent would be expected to exert a deleterious effect upon some viruses. Some investigations have been made into the viricidal activity of acetone in order to determine the safety in handling sections of infected material fixed with acetone for microscopic studies.

Among the ether-labile viruses the infectivity of influenza virus was destroyed within 10 sec when the virus was exposed to 90 percent acetone (Ref. 20) but the infectivity of West Nile virus was not destroyed by an exposure of 24 hours to acetone (Ref. 25). Respiratory syncytial virus was rendered noninfectious by exposure to acetone at 5°C for 10 min but not for 10 sec (Ref. 26). Yellow fever virus was rendered noninfectious by an exposure of less than 1 hour to acetone at -60°C (Ref. 27) but Rift Valley fever and Venezeulan equine encephalomyelitis viruses were still infectious after an exposure of 48 hours (Ref. 27). On the other hand Rift Valley fever virus was reported to have lost is infectivity for mice after contact with acetone at -70°C for 18 hours (Ref. 28). Thus, among 6 ether labile viruses a considerable range in senstivity to acetone is evident.

Among the ether-stable viruses the infectivity of adenovirus 5 was not destroyed during an exposure period of 7 days to acetone at 5°C but there was a decrease in the titer of the virus (Ref. 20). As would be expected variola virus was not inactivated by acetone (Ref. 29). There was only a slight inhibition of the replication of vaccinia and rabbit-pox viruses by either one percent acetone or

by 1 mcg per ml N-methyl-isatin-β-thiosemicarbozone but in the presence of both chemicals in the above concentrations there was a great reduction in the infectivity of the viruses (Ref. 30). Psittacosis virus lost its infectivity after exposure to acetone at -60°C for 4 hours (Ref. 27). Thus among 5 ether-stable viruses a considerable range in sensitivity to acetone exists.

The mechanism of antiviral action of acetone on one virus has been studied in detail. By some obscure process acetone prevents the formation of complete, infectious virions of rabbit-pox virus. Acetone in the concentration of one percent exerts no significant influence on production of early viral messenger ribonucleic acid, formation of polyribosomes, deoxyribonucleic acid replication or protein synthesis. Instead of normal virions being assemble, noninfectious virions are produced (Ref. 31).

Against the one bacterium, Aerobacter aerogenes, on which the mechanism of action of acetone was studied, it was concluded that the bacteriostatic action of acetone was due to the inhibition of production of metabolites essential for rapid cell division (Ref. 32).

Against rickettsia, acetone at -60°C rendered Coxiella burneti noninfectious within 24 hours (Ref. 27).

Due to its solvent action, rapid evaporation and lowering of surface tension which provide better contact with tissues and micro-organisms, acetone is frequently added to alcohol for the vehicle for topical antimicrobial drugs. Ten percent was the smallest amount of acetone that was found to satisfactorily defat skin and this has become the concentration most commonly used. Fifty percent ethanol was found to be satisfactory as lower concentrations showed a rapid decrease in disinfecting power and higher concentrations did not show sufficient increase in disinfecting power to justify the added expense (Ref. 33). Alcohol (52.5 percent V/V)-acetone (10 percent V/V)-water mixture killed Staphylococcus aureus, 2 strains of Streptococcus pyogenes and Escherichia coli in less than 1 minute (Ref. 34).

Not only has the alcohol-acetone mixture demonstrated rapid bacteriocidal action in vitro but it has been found to be highly effective in destroying bacteria on the skin. It has been reported that the alcohol-acetone mixture destroyed 96 percent of the bacteria on the skin (Ref. 35). This does not leave room for much improvement by adding additional substances to the alcohol-acetone mixture for the sole purpose of destroying bacteria on the skin.

Information on several products containing acetone were submitted to the Panel (Ref. 44) and each submission has been examined.

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(44) OTC Volumes: 160004, 160007, 160010, 160097, 160148, 160157, 160186, 160189, 160190.

2. Methyl ethyl ketone

Methyl ethyl ketone is a flammable liquid with an acetone-like odor. It is miscible with alcohol, ether and benzene. It is soluble in about 4 parts of water (27.5 percent). If forms a constant boiling mixure with water, boiling point 73.4°C, that contain 88.7 percent methyl ethyl ketone (Ref. 1). It is widely used as a solvent and is stated to be among the safest solvents for substances to be used for skin sensitivity testing (patch test) (Ref. 2).

Metyl ethyl ketone is considered to be only moderately toxic with a probably oral lethal dose for an adult to be 0.5 to 5 gms/kg. The vapors are irritating to mucous membranes and conjunctiva (Ref. 3). The Threshhold Limit Value (TLV) of methyl ethyl ketone in air is stated to be 200 ppm (Ref. 4).

The limited investigations on methyl ethyl ketone indicate that it has weak bacteriostatic and bactericidal activities. The growth of Escherichia coli was inhibited for 48 hours at 37°C by a 1:40 dilution and that of Pseudomonas fluorescens non-liquefaciens by a 1:35 but not by a 1:50 dilution (Ref. 5). The phenol coefficients against Staphyloccoccus aureus and Salmonella typhosa have been reported to be 0.080 and 0.102, respectively (Ref. 6).

Information on products containing methyl ehtyl ketone was submitted to the panel (Ref. 7) and each submission has been examined.

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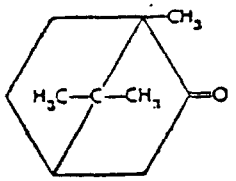
(7) OTC Volume 160018.

3. Camphor

Camphor is a ketone (concrete volatile oil) that was originally obtained from the tree Cinamomum camphora (Linne) Nees et Ebermaier. It appears in colorless to white, translucent, tough masses with crystalline fracture or granules that volatilize slowly at ordinary temperatures. Its chemical formula, $C_{10}H_{16}O$, is represented as follows:



Camphor

One gm is soluble in 0.4 ml acetone, 0.5 ml chloroform, 1 ml alcohol, 1 ml ether and about 800 ml water. It is readily soluble in fixed and volatile oils. It liquefies when triturated with menthol, phenol or thymol (eutectic mixture). It has a peculiar tenacity and cannot be powdered in a mortar unless it is moistened with an organic solvent. Currently much of the camphor is produced synthetically. The natural product is dextrorotatory while the synthetic product is optically inactive, the racemic form (Refs. 1, 2, and 3).

Camphor has a characteristic, penetrating odor. Its taste is slightly bitter, aromatic and cooling. A small oral dose may produce the sensation of warmth in the stomach while larger doses may produce nausea and vomiting (Ref. 4).

Although it is stated that camphor is readily absorbed from all sites of administration (Ref. 4) no evidence has been found that it is absorbed through the skin to any great extent. It is absorbed through the mucous membranes of the respiratory and gastrointestinal tracts and from subcutaneous and intramuscular deposits. Upon entering the system the following symptomatology is produced:

a. Nausea and vomiting.

b. Feeling of warmth. Headaches.

c. Confusion, vertigo, excitement, restlessness, delirium, and hallucinations.

d. Increased muscular excitability, tremors, and jerky movements.

e. Epileptiform convulsions, followed by depression. The convulsions sometimes appear early in the syndrome and may be severe but they do not have the grave prognosis of strychnine convulsions.

f. Coma. Central nervous system depression which may at times be the primary clinical response.

g. Death may result from respiratory failure or from status epilepticus.

h. Slow convalescence during days or weeks accompanied with persistent gastric distress.

Vomiting has been reported occurring immediately or within 5 minutes after ingestion of camphorated oil or it has been delayed as long as 2 hours. Likewise, convulsions have occurred within 4 minutes or after hours following the ingestion (Ref. 5). The vomiting, either spontaneous or induced, has been responsible for saving many lives as has stomach lavage.

Upon entrance to the body by whatever means, camphor is reduced and hydroxylated, conjugated with glucuronic acid, probably in the liver, and excreted by the kidneys (Ref. 6). The injection of camphor into cats usually elicited a more or less transient strengthening of their respiration but with no substantial changes in the blood oxygen saturation and the carbon-dioxide levels of arterial blood remained within normal limits. Subcutaneous and intravenous injection of camphor did not exert any substantial influence in the cerebral blood supply in cats. However, intraarterial injection of 1 mg camphor delivered in the direction of the brain product an elevation of blood flow. Subcutaneous injection of camphor reduced the pressure in the arteries constituting the circle of Willis and simultaneously dilated the pial arteries. It is quoted by the investigators that camphor is a cholinolytic agent that blocks the effect of acetylcholine on the heart and organs consisting of smooth muscle while at the same time

it is synergistic with adrenaline. In vitro, camphor in dilutions of 1:1000 or 1:3000 was stated to inhibit cerebral tissue respiration (Ref. 7).

The epileptiform convulsions and other clinical symptoms of the effect of camphor upon the central nervous system and persistence of violent headache have been taken as evidence of cerebral irritation (Refs. 8 and 9). Only a few of the fatal cases of camphor poisoning have been necropsied and usually the brain was not examined. The case of a male infant 19 months of age who died 5 days after swallowing an estimated one teaspoonful of camphorated oil (0.8 gms camphor) has contributed evidence of brain damage. The child vomited within a few minutes and again after hospitalization so the actual dose of camphor was less than that swallowed. Convulsions occurred and the supportive therapy that was administered perhaps prolonged life and allowed the pathological changes due to the camphor to develop. The necrospy revealed a swollen and soft brain. Microscopically there were extensive degenerative changes in the neurons. Neuronal changes were prodcued in mice but not in rabbits by the injection of camphor (Ref. 10). The autopsy on an 18 year old girl who died of acute camphor poisoning following the nibbling on pieces of camphor revealed a slight and uniform congestion of the brain as the only abnormal finding (Ref. 18).

It is difficult to estimate the lethal dose for man since vomiting usually occurs after ingesting camphor. The lethal doses of camphor for mice and rats by subcutaneous injection of 20 percent solution of camphor in olive oil have been listed as 2.2-2.4 and 2.2 gms/kg, respectively . The LD_{50} for rats by intraperitoneal injection is given as 0.9 gm/kg (Ref. 11). Convulsions but not death were produced in rabbits by the administration of 0.28-0.56 gm/kg by stomach tube (Ref. 6). In studies of the influence of age on the susceptibility of rats to camphor it was found that the proportion of animals convulsing and the average number of cnvulsions did not vary among the various age groups (4 months to 19 months) but there was increased variability in the number of convulsions in the oldest age group (Ref. 12). A male child 16 months of age died 7 hours after receiving one teaspoonful of camphorated oil (containing about 0.8 gms camphor) in error for cough medicine. The stomach was lavaged in perhaps an hour after the ingestion of the camphor and numerous droplets of oil were present in the washings. The patient was autopsied (Ref. 13). Assuming that a male child of 16 months weighs about 11 kg (Ref. 14) this makes it possible to estimate that the lethal dose of camphor in this case was less than 0.07 gm/kg. Another male child, 19 months old, swallowed an estimated teaspoonful of camphorated oil and died in 5 days. The infant vomited material that smelled of camphor

(Ref. 5). Assuming that a male child of 19 months weighs at least 11.5 kg, this places the estimated lethal dose again at about 0.07 gm/kg. Approximately 2 gms camphor was reported lethal for a child 18 months old (Ref. 15), an estimated 1 dram (4 gms) camphor was fatal for a 16 month old female child (Ref. 16) and an estimated 0.5 dram (2 gms) was fatal to a female child 2 years 8 months of age in spite of vomiting and stomach lavage (Ref. 17). The approximate minimum lethal dose (MLD) for a 150 pound man is stated to be 2 gms (Ref. 19) which is about 0.03 gms/kg. Thus it is evident that man is more susceptible to camphor than mice, rats or rabbits.

Workers exposed to the synthetic camphor in a packaging plant for 8 hrs/day, 5 days/wk did not experience reactions to camphor, such as irritation to the eyes and nose and loss of smell, when the concentration was approximately 2 parts of camphor to 1 million parts of air which is about 12.4 mg/cubic meter. Exposure to concentrations of 29 to 39 mg camphor/cubic meter of air for short periods of time produce slight irritation of the eyes and loss of smell. These symptoms disappeared in about 10 minutes after exposure to fresh air (Ref. 35).

No reports of allergic reactions to camphor have been found in the scientific literature.

An Over-the-Counter commonly used cold remedy and decongestant containing Camphor, Menthol, Thymol, Spirits of Turpentine, Eucalyptus oil, Cedar leaf oil and Myristica oil was reported to impair the clearance of aerosolized Staphylococcus aureaus from the lungs of mice (Ref. 20). The mice were exposed to the vapors of the product for periods of up to 12 hours prior to the challenge with the staphylococci and the depression of the defenses of the animals generally was proportional to the amount of the product added to the vaporizing solution. (Degrees of depression of the clearing mechanisms not stated as the communication is an abstract of a paper presentaed at a scientific meeting.) Untreated mice inactivated 87.4 $\pm$ 1.8 percent of the inhaled staphylococci 4 hours after being infected while the mice trated by topical application of the product inactivated 68.4 $\pm$ 5.3 percent.

The above results were not substantiated by another group of investigators (Ref. 21). Mice were exposed prior to staphylococcal challenge for 12 hours to vapors up to 30 times the clinical atmospheric concentration of the vapors of this product. The volatile aromatic components of the product, camphor, menthol, eucalyptol and α and β pinenes were monitored by gas chromatography. Treated and untreaed control mice were challenged with aerosols of S. aureaus. Some animal

were sacrificed immediately after challenge and others were sacrificed 4 hours later. The vapor components of the product did not significantly depress the pulmonary antibacterial activity against S. aureus. The product was not applied topically as in the preceeding experiments. Since there are no data in the scientific literature demonstrating that camphor is or is not absorbed through the skin, it must still be assumed that camphor applied topically or as an aerosol does not depress the pulmonary antibacterial activity of mice against S. aureus.

A child 6 weeks old developed a chemical pneumonitis following being sprayed in his face with an aerosol containing camphor, menthol, thymol, eucalyptol, and naphthalene (Ref. 25). It is difficult to decide which of the ingredients was the causative agent, if any of the ingredients was causative agent. Of the ingredients, camphor is the most readily absorbed from the mucous membranes and the most toxic.

Concerning camphor as a decongestant, very little vasoconstrictive effect on the nasal mucosa was detected by means of a plethylsomograph after spraying one naris with 1, 2 or 5 percent solutions of camphor in liquid petrolatum (Ref. 22). A group of 10 rabbits received a nasal srpay of 5 percent camphor in liquid petrolatum daily for 9 months.

After the fourth week the animals showed alternately a serous and a purulent discharge. Autopsies of the surviving animals at the end of the 9 months of treatment showed evidence of a purulent rhinitis which was only slightly more involved than that in the control animals that were sprayed with the solvent, liquid petrolatum (Ref. 23). Thus camphor, up to a concentration of 5 percent, has very little vasoconstrictive action and is only slightly more irritating than liquid petrolatum to the nasal mucosa when applied over a long period of time.

A one percent solution of camphor in liquid petrolatum has no apparent effect upon the ciliary action of normal mucous membrane but neither does liquid petrolatum. The difficulty appears to be that the oil does not come in contact with the cilia, being separated from them by mucus (Ref. 24).

There have been four instances of camphor poisoning during pregnancy. The mothers survived but in one case the infant died 30 minues after birth and in two cases there is evidence that camphor crossed the placental barrier.

The first case o camphor poisoning during pregnancy was reported in 1957 (Ref. 26). A 32 year old woman in her third month of gestation was accidently given 45 ml camphorated oil (containing 9 gms camphor)

by a nurse's aid instead of mineral oil. She vomited almost immediately, then had a convulsion and became unconscious. Gastric lavage and treatment with oxygen and pentobarbital sodium were immediately instituted. She responded promptly to treatment, regained consciousness after an hour and recovered without any apparent further ill effects except for nausea that persisted for several days. A normal infant was delivered at term.

The second instance of camphor poisoning during pregnancy was a 17 year old girl who drank 2 oz camphorated oil (estimated 12 gms camphor) in an attempt to produce abortion. She began to vomit soon thereafter and had stomach lavage 2 hours following the ingestion. The patient recovered and no further details were provided (Ref. 27).

The third case of camphor poisoning during pregnancy was reported in more detail (Ref. 28). A 20 year old woman, 40 weeks pregnant, ingested 15 gms camphorated oil (estimated 3 gms camphor) that had been purchased erroneously for castor oil to induce labor. The patient was discovered 15 minutes later prostrate and in an agitated and irrational state. Prompt and strong medical procedures alleviated the symptoms within a few hours. Labor began spontaneously 17 hours after ingesting the camphorated oil and 9 hours later a limp, cyanotic female was delivered who lived only 30 minutes. Camphor was detected in the maternal circulation 15 minutes after ingestion of the camphor but

not after 8, 20 or 36 hours. It was not present in the placental blood when tested at 20 and 36 hours but it was in the cord blood when tested at 36 hours. Camphor was present in the amniotic fluid when tested 20 and 36 hours after its ingestion and in the brain, liver and kidney of the infant at time of birth which was 36 hours after ingestion. Thus camphor is capable of crossing the placental barrier.

The fourth reported case of camphor poisoning during pregnancy was a mother who accidently took 2 oz camphorated oil (containing about 12 gms camphor) thinking she was taking castor oil. Nausea and a convulsion occurred 20 minutes later. After the third convulsion gastric lavage and anticonvulsant therapy were instituted. An apparently healthy infant was delivered 20 hours later but with the odor of camphor detected from the skin and mouth. By means of gas chromatography blood samples taken 24 hours post ingestion of the camphor showed just detectable amounts of camphor in the infant's blood but large amounts were detected in the mother's blood. The amniotic fluid had a distinct odor of camphor. This is the second case in which camphor crossed the placental barrier (Ref. 29).

The cases of poisoning following the ingestion of solid camphor are of interest because its absorption is not aided by alcohol or oil as solvents. It is soluble only to the extent of 1 part in 800 parts

of water so solution in the gastric juices is limited. Between 1833 and 1898 there were 7 cases of poisoning reported following the ingestion of solid camphor and 2 of these cases, a 20 year old man and a child 2 years 8 months old, died. A case mortality rate of 28 percent in this limited series.

A physician consumed an estimated 120 gr (8 gms) camphor mixed with sugar during the course of an evening for a cold remedy and survived without vomiting or symptomatic therapy (Ref. 30). A young man 20 years of age swallowed bits of camphor to the extent of 2 drams (about 8 gms). He vomited bits of camphor and survived with the aid of symptomatic therapy (Ref. 31). A 24 year old man ate 2 pieces of camphor, each about the size of a nutmeg. He vomited, had convulsions, received supportive therapy and survived (Ref. 32). A girl 18 years old nibbled on pieces of camphor late in the evening, vomited during the night and expired between 3 and 4 A.M. The only abnormality observed at autopsy was slight and uniform congestion of the brain (Ref. 18).

After an adult ate an estimated 11.7 gms pure camphor, symptoms of nausea and dizziness appeared in about 30 minutes followed shortly with a ringing in the ears, loss of consciousness and convulsions.

The patient vomited 2.25 hours after eating the camphor and bits of camphor were in the vomitus so the amount of camphor entering the circulation is unknown (Ref. 33). A female child 2 years 8 months of age ate an estimated 2 gms solid camphor. She was seized with convulsions in about 15 minutes and died in about 18 hours. Although vomiting was induced and stomach lavage was employed, the measures apparently did not remove sufficient of the camphor to prevent a lethal dose (Ref. 17). A 16 year old boy nibbled on some solid camphor and developed great nausea, convulsions, violent deliriums and a livid face. Recovery occurred following therapy (Ref. 34).

Although camphor is classified as a very toxic substance (the oral lethal dose for humans is stated to be 0.05 to 0.5 gm/kg (Ref. 4), the solid form of camphor has posed no great health threat for many years, perhaps due to the less frequent use of camphor for moth repellent, deodorizer, etc. Likewise the alcoholic solution of camphor poses no great health problem. Between 1887 and 1898 three cases were reported and 1957 the fourth case of camphor poisoning due to the ingestion of the alcoholic solution of camphor was reported. The alcoholic solution, Tincture of Camphor or Spirit of Camphor, contains 10 percent camphor in 80 to 87 percent ethanol (Ref. 36).

After swallowing some alcoholic solution of camphor a 10 year old child became unconscious in about 30 minutes. Convulsions occurred shortly thereafter and in about 2.5 hours he was comatose. Death occurred about 4 hours after swallowing the camphor which was estimated to be about 1 gm (Ref. 37). A young woman took an overdose of spirits of camphor for a cold remedy. She developed giddiness and noises in the head, became delirious, frantic and maniacal and had to be restrained by force. She recovered after strong therapeutic measures (Ref. 34). Following the ingestion of spirit of camphor a young girl developed vomiting, convulsions, a livid face and frothing at the mouth. Recovery occured following sedation (Ref. 34). A 2 year old child drank about half an ounce of spirit of camphor (about 1.5 gm camphor). He was rushed to a hospital and made a complete recovery (Ref. 38). Thus in this small series of 4 cases of poisoning due to an alcoholic solution of camphor there was one death, a case mortality rate of 25 percent which is comparable to that mentioned above for solid camphor.

Camphorated oil, or camphor linament, a 20 percent solution of camphor in cotton seed oil, has been and continues to be the most frequent cause of camphor poisoning. It has been administered most often to children, occassionally to adults, in error by parents,

a prison attendant, and nurse's aid and even supplied in error at a drug store. It most commonly has been mistaken for castor oil, but on occasions it has been mistaken for cod liver oil, a cough remedy, olive oil and mineral oil. The misery, anxiety, hospitalization and even death could have been avoided in the majority of cases by appropriate safety measures as can be seen by the reports of camphor poisoning in the scientific literature.

A woman took on an empty stomach 2 tablespoonfuls camphorated oil in error for castor oil. Vomiting was induced and the patient recovered (Ref. 39). A child 2 years 9 months old developed convulsion about 15 minutes after swallowing some linamentum camphora. He was revived from an almost moribund condition by means of stomach lavage (Ref. 39). A child 1 year 10 months of age received a small teaspoonful camphorated oil (equivalent to about 0.8 gm camphor) which was mistaken for a cough remedy. The first symptom was a convulsion that occured in about 20 minutes and unconsciousness lasted for another 30 minutes. Vomiting and symptomatic treatment brought about recovery (Ref. 15). It was stated in the same report without specific literature citation that approximately 2 gms camphor had proved fatal to a child 1 year 6 months old and about 1.3 gms had produced severe symptoms in an adult. Some fatal poisonings due to camphor are mentioned in an early (1906) textbook on therapeutics (Ref. 41). The possible

persistence of the effects of camphor poisoning is illustrated by the 45 year old woman who took by mistake for castor oil 4 drahms camphorated oil containing about 50 grains of camphor. Symptoms started 1.5 hours later. Vomiting, induced after 2 hours produced little oil and the odor of camphor was present in the vomitus. A physician administered stimulants. However, 5 days after taking camphor the patient was mentally depressed, nervous and apprehensive, mouth and skin dry, finger tips and lips slightly cyanotic, skin pale and superficial veins apparently empty, pulse quite irregular and respiration rapid and shallow. For several weeks attacks of tachycardia came on frequently without apparent cause and accompanied by mental depression (Ref. 42). Following the ingestion of camphor in the form of a homeopathic alcoholic solution, nervous sequelae continued for several months in a young lady, and a clergyman was unable to work for 2 months (Ref. 82).

Among 4 cases of camphor poisoning, one was a 2 months old child who was given camphorated oil in error for cough medicine since both preparations were in similar brown bottles, another was a 12 year old boy who was given camphorated oil instead of castor oil, and another case was a 33 year old woman who ingested 4 oz camphorated oil that had been given to her by a pharmacist for castor oil. All individuals received medical attention in hospitals and the woman was in intesive care for 4 days. It was pointed out that more than 300

cases of camphor poisoning are reported each year to the National Clearinghouse for Poison Control Centers and the incidence has increased each year for the past 5 years (Ref. 83).

A child, aged 1 year 4 months, while playing with a bottle of camphorated oil, swallowed some and it was estimated that about 4 gms of camphor were consumed. Vomiting occurred after 1 hour and convulsions after 1 hours 20 minutes. In spite of stomach lavage and the use of antispasmotics, the child died in less than 12 hours (Ref. 16). A robust 18 month old child was given by mistake 1 teaspoonful camphorated oil immediately after a full supper of milk and cereal without any unfavorable effects. The child received castor oil as a prophylactic measure 2 hours after recieving the camphorated oil (Ref. 43). This is in contrast to the 16 month old child who died 7 hours after receiving 1 teaspoonful camphorated oil in error for castor oil (Ref. 13). Another child is mentioned who received the same dose of camphor in oil, vomited soon thereafter and showed no ill effects.

Camphor poisoning has not always occurred in isolated cases. A group of 20 children was given camphorated oil mistaken for castor oil. Each child received an estimated 3 to 4.4 gms camphor since the

doses were varied according to the age of the children which was 4 to 10 years. Symptoms began appearing in 45 minutes. Vomiting was induced. Recovery occurred within 20 minutes but the most severe cases were comatose for 20 hours and recovery occurred in 29 hours (Ref. 44). The following 7 cases of poisoning due to camphorated oil occurred in children, whose ages ranged from 15 months to 12 years, after ingesting the equivalent of 0.8 to 3 gms camphor. Three children in the same family, ages 1, 10 and 12 years, were each given a teaspoonful camphorated oil (0.8 gms camphor) that had been supplied erronerously at a drug store for castor oil. The children immediately vomited and recovered. A 7 year old girl swallowed a tablespoonful camphorated oil intended for castor oil (3 gms camphor), was rushed to a hospital and recovered. A 2 year old boy drank about 2 teaspoonfuls camphorated oil (1.6 gms camphor), was taken to a hospital and recovered. A 1 year 3 month old child swallowed a teaspoonful of camphorated oil, had the usual symptoms of camphor poisoning and recovered. A 1 year 6 month old child was found playing with a bottle of camphorated oil and covered with the oil. She was rushed to a hospital and expired 4 hours later. The amount of camphor to which the child was exposed was undetermined (Ref. 38).

A girl aged 10 years, who was slightly mentally deficient, took orally some camphorated oil (equivalent to about 5 gms camphor) and convulsed. The stomach was lavaged. The temperature was elevated for 3 days, she complained of severe headache and there was retraction of the head. Recovery occurred following a lumbar puncture (Ref. 9). A child 20 months old swallowed an unknown quantity of camphorated oil. He was found unconscious with muscle twitching and profuse salivation. There is no record of vomiting or stomach lavage but the throat was aspirated. He recovered after symptomatic treatment (Ref. 45). A 44 year old man was given an ounce of camphorated liniment (about 6 gms camphor) by a prison attendant in the evening in error for castor oil. He was discovered in a convulsion 1.75 hours later. He soon became semidelirious with twitching of the lower extremities. Therapy consisted of gastric lavage. In the morning he remembered nothing after taking the liniment and was surprised to find himself in the hospital from which he was discharged on the third day (Ref. 46).

An adult male mistakenly took 1.5 oz camphor liniment (equivalent to 9 gms camphor) which was provided by a drug clerk for olive oil. Within an hour he had a convulsion that lasted for 5 minutes and subsequently lasped into unconsciousness which lasted for half an hour.

Vomiting occurred thereafter and the patient recovered (Ref. 47). Complete recovery is not always rapid as evidenced by a 20 year old woman who took by mistake 2 oz camphorated oil (approximately 12 gms camphor). In about 50 minutes she developed nausea and vomiting which were followed by violent convulsions. The stomach was lavaged and the patient sedated. Recovery supposedly was uneventful but on the fourth day she was readmitted to the hospital with the complaint of violent headache, malaise and anorexia. The blood pressure was elevated. Treatment was symptomatic and the blood pressure returned to normal within a week. Cerebral irritation was considered because of the persistent headache and elevated blood pressure (Ref. 8).

A male child 14 months old was given a brimming teaspoonful of camphorated oil (approxiamtely 0.8 gm camphor) by mistake for cod liver oil. Almost immediately thereafter he was given 1.5 cups milk. The first symptoms of camphor poisoning appeared in about 20 minutes. Within 45 minutes his condition worstened and only by such heroic efforts as artifical respiration, inhalation of oxygen and carbon dioxide and injections of adrenaline was death prevented (Ref. 48).

There have been a few reports on the incidence of camphor poisoning over a period of time. During a 4 year period, 1944-1948, among 250 consecutive admissions to the Children's Hospital of Washington, D.C., for acute poisoning by ingestion, which represented 1.07 percent of the total number of admissions during that period, camphor and lye were the third most frequent poisons and each accounted for 14 cases. Camphorated oil, a linament and a salve accounted for 10, 3 and 1 case, respectively (Ref. 49). As is so often the case, in the majority of the instances the accident was on the part of the parent rather than the child which indicates where the safety measures need to be directed. In several cases camphorated oil was given when castor oil or cod liver oil was intended.

During the period of 1931-1951, 502 recorded cases of accidental poisoning in children under the age of 12 years at two hospitals in Scotland were examined. The information on 545 fatally poisoned children in Britain was also included (Ref. 50). In the Scotland cases camphor headed the list of medicines intended for external use, excluding atropine, that produced poisoning upon ingestion, with 29 cases. Iodine was second with 11 cases out of the total 68 cases. However, in Britain, in this same category of cases, camphor was responsible for 12 deaths, being exceeded only by methyl salicylate (oil of

wintergreen) which caused 36 deaths. Among the 29 cases of camphor poisoning mentioned above there were 12 deaths for a case mortality rate of 41 percent (Ref. 5). Case histories were available for only 19 of the victims. The ages of the patients ranged from 13 months to 9 years but 16 of the patients were less than 3 years old. All received camphorated oil in doses of 1 dr (1 teaspoonful) to 1 oz which represents doses of camphor ranging from 0.8 to 6.2 gms. In 11 of the 19 cases the camphorated oil was given in error by the parents.

There is one reported case in which the ingestion was the result of swallowing material instilled into the nostrils for a cold remedy. A 48 year old nurses' aid instilled camphor containing nose drops at least twice into each nostril using a half-ful bottle (7.5 ml) of the medicament. The material was allowed to trickle down the throat and was swallowed. Evidence of poisoning was apparant in 2.5 hours and in about 4.5 hours she had an epileptiform convulsion. Vomiting began after 5 hours and the vomitus had a strong odor of camphor and contained oil. She was able to return to work after several days (Ref. 57).

A 16 month old female child swallowed about 1 tablespoonful camphorated oil (about 3 gms camphor). Although vomiting was induced

immediately the child had a convulsion lasting about 20 minutes and a second seizure occurred on the way to the hospital. Following stomach lavage and supportive therapy the child was discharged after several days of hospitalization (Ref. 52).

A group of 7 cases of camphor poisoning was reported from New York City in which the victims ranged in age from 10 months to 17 years. The episodes followed the consumption of varying amounts of camphorated oil representing the ingestion of 0.8 to 13 gms camphor. Vomiting occurred in each case and stomach lavage was performed in 6 of the cases. These measures either accounted for or contributed to the recovery of each individual (Ref. 21). However, it has been reported that vomiting was not a symptom in 53 percent of 97 cases reported during 1955-1956 (Ref. 53). Details of the 7 cases point out where certain safety measures could have been important in preventing the accident.

In one case a mother gave her 4 month old infant 1 teaspoonful camphorated oil (containing about 0.8 gms camphor) mistaken for a cough medicine since both preparations were in bottles of identical size and shape. The child began voimiting immediately and stomach lavage was carried out in a hospital. A 7 year old child was given 1 tablespoonful camphorated oil (containing abot 3 gms camphor)

mistaken for castor oil. Spontaneous vomiting occurred within 15-30 minutes and her stomach was lavaged in a hospital within 1 hour. Another case was a 2.5 year old child who swallowed about 0.5 oz camphorated oil (containing about 3 gms camphor). Vomiting was induced by the mother and at a hospital. Two cases involved a 3 year old boy and his 4 year old sister. Each swallowed an estimated ounce camphorated oil (containing about 6 gms camphor) and although the mother induced vomiting and their stomachs were lavaged at a hospital within 45 minutes of ingesting the camphor both became stuporous and developed convulsions. Both recovered after 3 days in the hospital with symptomatic and supportive therapy. A 17 year old girl drank 2 oz camphorated oil (containing about 12 gms camphor) in an attempt to induce abortion. Spontaneous vomiting occurred soon thereafter and her stomach was lavaged at a hospital within 2 hours. The seventh case was a 10 month old infant who drank about an oz of camphorated oil. The infant vomited spontaneously. Gastric lavage and symptomatic therapy were carried out in a hosptial.

A 3 year old girl swallowed an estimated tablespoonful of an OTC product (4.81 percent camphor). A convulsion occured 2 hours after ingesting the estimated 0.7 gms camphor. Serum drawn 7 hours after

the ingestion contained 1.95 mg camphor per 100 ml as determined by gas liquid chromatography but the 21 hour samples of serum and spinal fluid contained no detectable camphor. An electroencephalogram 18 hours after the seizure suggested a diffuse neuronal disturbance with excessive slow activity in the bianteriar and bicentral regions with no specific paroxysmal discharges. A repeat electroencephalogram 15 days later was unchanged but was normal after 3 months (Ref. 54).

During the period of 1970-1972 there were 175 admissions to the Newcastle Upon Tyne General Hospital for the ingestion of poisons by children of 6 months to 5 years of age which constituted 9.5 percent of the total admissions within this age group. Ten (5.7 percent) of these cases of poisoning were due to the ingestion of camphorated oil. There were no fatalities (Ref. 55). During 3.25 years (including the period of 1970-1972) 4 of 294 cases of poisoning in children admitted to another English hospital were due to the ingestion of camphorated oil (Ref. 56).

A 77 year old man took approximately 60 ml camphorated oil (approximately 12 gm camphor) that he had mistakenly received from a pharmacy for a cough elixir. The patient had catracts of sufficient

severity to prevent his reading the label on the bottle of camphorated oil. About 30 minutes later he vomited and had a grand mal seizure. Hemodialysis against soybean oil was started 4 hours after the ingestion and continued for 4.5 hours. Analysis of the oil by gas chromatography revealed 6.56 gm camphor. The patient was discharged from the hospital the following day with no apparent residual effects of his camphor intoxication (Ref. 59).

In the case of adults camphorated oil has been taken deliberately in attempted suicide. A man took 150 ml camphorated oil (an estimated 30 gms camphor) which is in the range of 6 to 14 estimated lethal doses for a person. Vomiting, gastric lavage and intesive supportive treatment brought about recovery in 36 hours (Ref. 57).

It becomes obvious from the cases of camphor poisoning reported in the scientific literature spanning a period of more than 100 years that safety measures dealing with the handling of camphorated oil need to be directed to adults. If not for the mortality the morbidity caused by camphorated oil justifies some changes in its handling. There is no specific antidote for camphor poisoning so prevention becomes more important. As long ago as 1897 it was recommended that a distinctive bottle and labeled poison be employed for camphorated oil (Ref. 15). Adequte poison warning was stressed in 1910 (Ref. 16).

It has been recommended that it be sold only by prescription (Refs. 29 and 52) but that would not necessarily prevent mistakes being made by the user in the home. Some control over sales has been advocated (Ref. 5) but with an estimated over 30 million ounces of camphor and camphorated oil being sold annually in the United States (Ref. 58) such restrictions would not necessarily adequately warn the user of the potential danger of the product. Discouragement of its use has been advocated (Ref. 27) and even removal from the market has been suggested (Refs. 57 and 58).

The eutectic mixture of equal parts of camphor and phenol was recommended for eipdermophytosis, "Athlete's foot," and cautioned against application to wet skin as water breaked down the mixture and the phenol becomes caustic (Ref. 60). In spite of the warnings serious burns resulted from individuals purchasing the product and treating themselves. One such report is that of a 30 year old woman who applied the mixture to the interdigitate areas of both feet. She was hospitalized for 13 days and totally disabled for 27 or 28 days (Ref. 61). A mixute of 3 parts phenol and 1 part camphor was applied to a fairly large area on the leg near the ankle and produced a necrotic area that required several weeks to heal (Ref. 62). Shortly after these

3 reports appeared a publication appeared extolling the advantages of treating pruritis ani due to mycotic infection with a mixture of equal parts of camphor and 95 percent phenol (Ref. 63). It was strongly advised by the proponent of this remedy that the area should be perfectly dry before applying the medicament and the treatment should be made only in the physician's office. In spite of these precautions the author stated that twice in his practice his patients had experienced burns due to the presence of moisture on the area of treatment. Since this treatment was recommended in 1944 there have been discovered better antifungal agents.

A report appeared recently of a 2 year old girl who ingested an estimated 1 or 2 teaspoonfuls of an OTC product contains 10.8 percent camphor and 4.7 percent phenol in an oil solution (estimated dose of camphor 0.43 to 0.86 grms). The child vomited immediately and was given egg white by her parents. Gastric lavage was carried out in a hospital until the odor of camphor was no longer detectable in the lavage fluids. A prelavage serum specimen drawn 20 minutes after ingestion of the camphor contained 0.0015 mg camphor per 100 ml as determined by gas liquid chromatography (Ref. 54).

Antipruritic or counterirritant action is one of the properties usually attributed to camphor. Camphor, phenol, menthol, tar and its derivatives (all in concentrations of 1 to 3 percent) are stated to be members of an older group of antipuritics for topical application that have the advantage of being cheap and readily available (Ref. 65). However, when camphor is in the concentrations of 1 and 2 percent in single component preparations and in 0.5 percent with 1 percent phenol in multiple component preparations no antipruritic action could be demonstrated against histamine-induced pruritis in human volunteers (Ref. 66).

Mild antiseptic or antiinfective activity is another property attributed to camphor. The slight solubility of camphor in water (1 part in about 800) and its weak antibacterial action precludes definitive in vitro antibacterial testing. Bacteriostatic action was not exerted against Staphylococcus aureus, Salmonella typhosa and Escherichia coli during an exposure to a saturated aqueous solution of camphor in nutrient broth for periods up to one week. No bactericidal action was evident against S. aureus and S. typhosa during an exposure period of 2 hours. However, when a solvent consisting of 31 parts each of alcohol, glycerine and water and 6.6 gms soap was used to prepare 1 and 3 percent solutions of camphor, an average phenol coefficient

of 0.74 was obtained with S. typhosa when the tests were carried out at 20°C and a phenol coefficient of 1.3 when the tests were carried out at 37°C. An average phenol coefficient of 0.5 with S. aureus was obtained when the tests were carried out at 20°C but no phenol coefficient could be determined when the tests were performed at 37°C because the solvent killed the microorganisms at that temperature (Ref. 67). It is reasonable to assume that at 20°C the solvent may have had an additive effect to that of camphor in the killing of S. aureus.

A definitive study on the effect of d-camphor on a camphor-sensitive strain of E. coli (strain 82/r, an adenine-dependent derivative of strain B/r) was made in which bacteriostasis was demonstrated but the bacteriostatic action was only temporary. In the synthetic culture medium employed with aerobic incubation, the strain had a generation time of 36 minutes, it had a lag period of 2 hours, followed by an exponential growth phase of 5 hours (mid-log occurring at 5 hours) and that followed by a stationary phase of 7 hours. The addition of d-camphor to a concentration of 530 μg/ml at the 5th hour of growth produced no apparent effect on the cell concentration during an observation period of 72 minutes. A concentration of 650 μg/ml showed a slight inhibition of growth. The first pronounced effects of camphor were at a concentration of 850 μg/ml. Here the total cell

numbers, viable cell numbers and optical density increased at normal rates for 10 minutes, after the addition of camphor, then the total cell numbers and viable cell numbers remained constant for the next 62 minutes (a period of bacteriostatis) while the optical density increased at a much reduced rate (indicating an increase in large cells). At a concentration of 1100 μg d-camphor/ml, which is nearly a saturated aqueous solution of camphor, the period of bacteriodstis lasted 7 hours and growth resumed thereafter. A halting of DNA, RNA and protein biosynthesis by the exposure to d-camphor indicated that the chemical interfered with a basic metabolic function upon which these synthetic processes depended (Ref. 68). The oxidative metabolism of glucose, pyruvate and succinate in whole cells of E. coli 82/r were inhibited by d-camphor to the extent of 50 to 65 percent (Ref. 69).

Adding d-camphor to a culture of Vibrio cholerae during the exponential growth phase indicated that a concentration of 500 μg/ml had no significant effect upon the microorganisms while at a concentration of 700 ug/ml the rate of growth was reduced for only 2 hours and thereafter the rate remained constant for 2.5 hours (the period of observation). At a concentration of 900 μg/ml d-camphor exerted

a bacteriostatic effect as the number of viable virios remained constant throughout the period of observation (4.5 hours). Only at a concentration of 1200 µg/ml (approximately a saturated aqueous solution of d-cmaphor) was there a slight decrease in the number of viable virios (a slight bactericidal action) during the period of observation which was 4.5 hours (Ref. 70).

Against fungi the action of campor is also very weak. A saturated aqueous solution of camphor killed pathogenic yeast-like organisms in 24 hours but not in 100 minutes as did other substances such as methol, turpentine, toluence and oils of eucalyptus and peppermint. Thymol and oils of cinnamon and clove were more active (Ref. 71). Upon studying a group of 20 fungi a final concentration of 1:1500 of camphor killed one of the fungi during a contact period of 60 minutes and killed only 7 percent of the fungus cultures after contact for 24 hours (Re.f. 72).

Using the enzyme invertase produced by yeast to split the disaccharide sucrose into dextrose and levulose during a period of 8 hours as a test system for antifungal activity, it was found that camphor was only 20 percent efficient in inhibiting the activity of the enxyme while the most efficient oils tested, those of wintergreen and cinnomon, were 44 and 48 percent, respectively (Ref. 73).

Camphor is categorized as anti-infective in the United States Pharmacopeia (Ref. 2) and stated to be somewhat anptic in the United States Dispensatory (Ref. 3). The results of in vitro testing published in the scientific literature do not support these claims as the saturated aqueous solution of camphor has only a transient bacteriostatic action. The therapeutic dose of a chemotherapeutic drug needs to be one-tenth or less of the toxic dose of the drug. The lethal dose of camphor for man has been estimated to be about 0.07 gm/kg. A saturated solution of camphor is about 1.25 gms/liter and that is incapable of killing or of even prolonged arresting the growth of a variety of pahtogenic microorganisms. Furthermore, the toxic dose of camphor for man is even less. A child who ingested an estimated 0.7 gm camphor vomited and had a generalized convulsion. A sample of serum collected 7 hours after the ingestion contained 1.95 mg camphor/100 ml (Ref. 54). This serum concentration of 0.0195 gm/l associated with symptoms of toxicity is about 1/64th the concentration of the saturated solution of camphor that has only a transient bacteriostatic action, no demonstrated killing action of infectious microorganisms and no demonstration of having prevented infection.

The claims that camphor is anti-infective and antiseptic are not valid and statements proclaiming such activities should be discontinued.

The mutagenic property of camphor appears to have been overlooked by editors and authors of compendia and reference books. The mutagenic action of camphor on fungi has been known since 1943 but its action has been studied more intensely with bacteria.

The cultivation of a virulent strain of Yersinia pestis (Pasteurella pestis) in the presence of 0.025 to 0.055 percent camphor incorporated into the culture medium produced no changes in colony morphology but the cellular morphology changed to "giant" cells that were twice as long and slightly wider than normal cells. The camphor-induced variants were as pathogenic for mice as the parent strain and were stable during 10 animal and 15 culture medium passages. The effective concentration of camphor inducing the mutation of the Yersinia cells may have been much less than that added to the culture medium since camphor volitalized rapidly at 37°C and the cultures had to be incubated 96 hours because of the growth-delaying action of the camphor. Possibly rapid penetration of camphor into the bacterial cells is an important factor under these conditions for the mutagenic effect (Ref. 74).

The growth of Escherichia coli, strain 82/r, in the presence of natural camphor vapors produced stable mutant strains of giant cells. One of these strains, designated P6 was stable in the absence of camphor for 2 years during repeated transfers, it produced colonies of coarsely

granular internal structure and the cells contained approximately three times greater amounts of DNA, RNA and dry weight than the parent strain (Ref. 75). The P6 strain was found to be much more resistant to X-rays, γ-rays and ultraviolet light than the parent 82/r strain (Ref. 76). Genetic studies suggest that only a single gene is involved in the mutation of the 82/r strain to the P6 strain (Ref. 77). Furthermore, by culturing in special culture medium segregants of the possible diploid strain of E. coli P6 were obtained that resembled the haploid E. coli 82/r strain.. By growing the segreants in the presence of camphor vapors stable giant cell froms similar to the P6 diploid type were obtained (Ref. 78).

Exposure to camphor has been employed to induce mutations in several fungi, examples are Aspergillus nidulans (Ref. 79), Penicillium notatum (Ref. 80), Torulopsis utilis (Ref. 81), Sordaria fimicola (Ref. 84) and yeasts (Ref. 87).

Not only is camphor a weak antimicrobial agent, at best, but some microorganisms are able to decompose camphor for a source of energy. One microorganism is a species of pseudomonad designated Pseudomonas putida and another is an unidentified gram-negative rod (Refs. 85 and 86).

Camphor thus becomes the first chemical, that has been used for decades as a topical anti-infective, antipruritic, analgesic and counter-irritant agent, to be shown to have mutagenic properties for bacteria and fungi and to be biodegraded by certain microorganisms.

As an irritant camphor has been shown to produce a weak stimulation of the phagocytic power of the skin (Ref. 88). When dissolved or suspended in white petrolatum, coal tar, histamine and ichthyol in concentrations of 0.5 percent, for example, produced a strong stimulation of the phagocytic power of the skin as judged by the ingestion of India ink particles from the blood by endothelial cells of the skin capillaries. In contrast, camphor produced only a mild stimulation and menthol and thymol produced no noticable effect. The material carrying the agents was of some importance. When an emulsifying base containing triethanolamine was employed instead of white petrolatum, coal tar, histamine and ichthyol were more reactive. Camphor was more reactive but still only weakly reactive and thymol but not menthol showed some reactivity.

The production of an irritation to counteract another irritation is not an effective means of relieving pain (Ref. 89). A rubefacient activity is sometimes claimed for camphor in compendia but tests

on human volunteers showed that an ointment containing 5 percent camphor produced only a slight erythema after 25 minutes and an elevation in skin temperature of only 0.1°Celcius after 30 minutes (Ref. 90).

Camphor and l-menthol were separately irradiated with tritium and the combined in an ointment to give a specific activity of 4.3 mc per gm of ointment. When 10 gms of the ointment were rubbed on the chest of a dog and the dog's nose positioned about 3 inches from the inuncted area, air collected from a bronchus just below the bifurcation was found to have 958 and 647 c.p.m. per cc of air after 8 and 12 hours exposure, respectively, to the vapors (Ref. 91). Thus camphor and menthol applied to the surface of the body within a few inches of the nostrils may give off vapors that may be inhaled and pentrate the respiratory tract at least past the bronchial bifurcation. Unfortunately the blood was not tested for radioactivity to determine if the vapors were absorbed into the circulation. Exposure to camphor vapors has been sufficient to produce mutations in E. coli (Ref. 75) so it is possible that inhalation of camphor vapors for hours could have mutagenic effects upon the respiratory bacterial flora.

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